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EXAMINER	
SAUNDERS, DAVID A	

ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 070,304	Applicant(s) DEBUS et al
	Examiner SAUNDERS	Group Art Unit 1644

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on 5/13/04.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disposition of Claims

☑ Claim(s) 1-23 is/are pending in the application.

Of the above claim(s) 18-21, 23 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 1-17, 22 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☑ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☑ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

Office Action Summary

Claims 1-23 are pending.

Applicant's election with traverse of Group I (claims 1-17 and 22) in the reply filed on 5/13/04 is acknowledged. The traversal is on the ground(s) that the burden to examine Group II would not be excessive. This is not found persuasive because applicant has presented a mere conclusionary statement as to the burden; as noted in the restriction requirement, the claims of Group II state nothing about the c-terminal of the receptor/selection moiety. These claims are thus drawn to a contribution over the art that must be different from that noted by the IPEA as providing a contribution to the claims of Group I.

The requirement is still deemed proper and is therefore made FINAL.

The examiner notes that claim 17 was amended on 3/5/02. This amended version is not drawn to the same limitations as original claim 17. The limitations of original claim 17 are thus in no claim under examination and will not be searched.

The disclosure is objected to because of the following informalities: at page 9, last paragraph, "selectrin" should be --selectin--.

Appropriate correction is required.

Claims 1-17 and 22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is confusing as to the functional relationships between the various recited elements.

One has an unclear idea what the scope of the "ligands" may be. Lines 3-4 in the preamble recite "endothelial and/or leukocyte ligands" whereas line 8 recites only "endothelial ligands."

At lines 6-7 "the signal unit" lacks antecedent basis, and this element has no clear function. It is not clear what is being "signaled." Is this "signal" what permits the "visualization" of line 1?

One has no idea as to what is meant by "the N-terminal end of the signal unit". In the art the term "N terminal" implies that there is a polypeptide that has amino acid residues at an N-terminal and a C-terminal. Applicant has recited various "signal units" in dependent claims 7-10 that are particles, and applicants exemplifications of these in the specification show dextrin coated particles (e.g. example 13); the examiner is baffled as to how such particles containing the "signal-unit" can be considered as having any "N-terminal."

Likewise, in dependent claims 11-12, applicant has recited various signal units that are metal ions. Applicant has disclosed that these can be complexed with a chelating agent having functional groups for coupling; see page 9, first paragraph. The examiner is again baffled as to how such chelators can be considered as having an "N-terminal."

In dependent claim 13, applicant has recited a signal unit that is "an-iodine containing molecule." Applicant has disclosed that these can be coupled to a chelator, which in turn binds a multi - His -L-selectin (page 9, last para.), presumably via a

coordinating Ni2+ ion; again, the examiner is baffled as to how this chelator is considered as having an "N-terminal".

Dependent claim 14 recites a signal unit that "contains a radionuclide." Example 5 embodies this as 123I coupled to a chelator, Newport Green. The examiner remains baffled as to how such a chelator is properly considered as having an "N-terminal."

Applicant has also contemplated use of dendrimers as vehicles for the delivery of chelating agents complexed with a paramagnetic metal or a metal (as is consistent with claims 11-12); see specification page 9, first para. The examiner fails to comprehend how either the chelating agent or the dendrimer can be properly considered as having an "N-terminal" end.

Dependent claim 17, as originally recited, referred to a coupling group that is a "polyhistidine radical." As the examiner understands the disclosure, at page 5, first para. and page 6, first full para., this radical is exemplified as being a C-terminal fusion moiety upon the receptor. This radical then functions as a coordinate binder of either Ni2+ or Co2+, which is complexed to a chelating agent, which is conjugated to the "signal unit"; again the examiner fails to envision the "chelator" as having any moiety which is an "N-terminal."

Dependent claim 15 recites that the signal unit contains a "dye molecule." Example 18 embodies an NIR dye coupled via its amino group to an oxidized L – selectin – Ig chimera (fusion protein). While an amino group has an N, it is not an "N-terminal" group according to the above stated art definition. The examiner is still baffled as to how any N-terminal group is thus embodied.

Claim 1, furthermore, concludes with the confusing limitation that the "N-terminal end of the signal unit that contains the binding domain is pointed away from the signal unit". Therein, the recitation of "the binding domain" lacks antecedent basis. Since the only previously recited element that one could envision as having binding domains is the "receptor" (of line 5), one would assume that "the binding domain" is within the receptor, but these concluding lines imply there is a "binding domain" within "the signal unit"; if so, what does this "binding domain" bind to?

In claim 1, line 8 "pointed away from" is unclear. The limitation that "the N-terminal end of the signal unit" is "pointed away from" the signal unit states nothing; any "end", whether "N-terminal" or of some other kind of functional group, must "point away from" the rest of the molecular structure of the signal unit. Thus, the limitation of "pointed away from" adds nothing that further sets forth the nature of the claimed invention.

Claim 2 is confusing by reciting "the receptor consists of at least 2 molecules." The embodiment thereof in example 3, of an L-selectin –Ig- chimera is stated as having "2 L-selectin per molecule". The examiner finds no teaching of any construct having "at least 2 molecules."

Claim 3 is confusing by reciting "at least two molecules". One does not know what element (the receptors or the signal unit) of claim 1 is considered to be " 2 molecules". Does applicant intend dependency from claim 2? At line 4, "chimera molecules" is unclear; one does not know what element of base claim 1 is chimeric (the receptor, the signal unit, or the 2 fused together); at line 4 "e.g." is indefinite; at lines 5-6

"Fab fragments" and "immunoglobulin skeletons" are unclear, because base claim 1 has recited nothing about any immunoglobulin or an Fab fragment thereof.

In claim 3, lines 2-3 "distance" is indefinite, because one does not know what distance is being measured -- e.g. between two N-terminal ends, or between the N-terminal end and the fusion point between the receptor and the signal unit?

Claim 16 is improperly multiple dependent by virtue of including itself in the multiple dependency.

Claim 22 fails to set forth the functional relationship between the various recited elements.

At line 6 "the signal unit" lacks antecedent basis and has no clear function. Does it provide a "signal" which permits the "visualization" of line 1?

At line 7 "the coupling" is unclear because the only previous recitation of anything being "coupled" is at line 5, which is referring to a coupling between the L-selectin and streptavidin. It appears that, at line? Applicant is referring to a different "coupling"; clarification of what is coupled to what is required.

Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant was not in possession of the genus of contrast agents recited in claim 1.

As noted above in the 112, second para. rejection of claim 1, it is unclear as to what is or is not embraced by the contrast agents of claim 1. The examiner has given a detailed explanation as to how numerous of the disclosed molecular constructs, that are consistent with the limitations of dependent claims 7-15, do not have "signal units" that can be properly considered as having an "N-terminal", as required by base claim 1. Therefore these exemplified constructs are not representative species of what applicant is attempting to describe as a genus in claim 1. Since claim 1 provided such a confusing description of the genus, the examiner considers that applicant had no clear idea of what the genus might be, when the application was filed.

Claims 1-17 and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an embodiment in which a "polyhistidine radical" is fused to the C-terminal end of a receptor/receptor fragment, does not reasonably provide enablement for other embodiments in which something other than a "polyhistidine radical" is fused to the C-terminal end of the receptor/receptor fragment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The examiner considers that the recitation of "the C-terminal end" in claim 1 refers to the C-terminal residue of the receptor/receptor fragment portion of the contrast agent. The disclosed polyhistidine "coupling group" is fused to the C-terminal of the receptor/receptor fragment. This limitation is required to be in the claims; otherwise; the only other possible point of fusion is at the N-terminal of the receptor. This is not consistent with claim limitations.

Furthermore, apart from the disclosed C-terminally fused polyhistidine, the examiner finds nothing in the disclosure which would limit the coupling of the receptor, via its C-terminal end, to the signal unit.

Applicant has contemplated biotin/avidin as coupling agents (e.g. recited in claim 22 and taught at page 6, second full para). However, applicant has not disclosed how the biotin/avidin is to be conjugated to the selectin, such that the conjugation occurs only at the C-terminal end thereof. The types of cross-linking reactions that are art known for the coupling of biotin/avidin to a protein involve certain amino acid residue side chains that are distributed throughout the protein sequence, from N- to the C-terminal. Applicant has therefore failed to provide adequate direction for one to conduct a coupling of biotin/avidin to only the C-terminal without undue experimentation.

Applicant has also contemplated the coupling of a signal unit (NIR dye) to a selectin – Ig G chimera that has been oxidized with periodate (example 18) the examiner considers that the periodate is employed to oxidize vicinal hydroxyl groups, within carbohydrate moieties. The examiner notes that, within the IgG segment of the exemplified chimera/fusion protein, any glycosylation would be in the CH2 domain; see Fig.16 of Fryer et al in Paul. The CH2 domain is not at the C-terminal of this chimera. Further, within the L-selectin segment of the chimera, there are seven potential glycosylation sites; see Pigott et al at page 102. These glycosylation sites would be even further than the CH2 domain toward the N-terminal of the chimera protein. The examiner thus finds nothing in Example 18 that shows one how to couple the "C-terminal end" of the selectin IgG chimera to the signal unit.

Claim 22 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the embodiment in which the contrast media detects endothelial ligands, does not reasonably provide enablement for the embodiment in which the contrast media detects leukocyte ligands. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. L-selectin is art known to mediate binding of lymphocytes and monocytes to a ligand on the endothelium. See Pigott it at page 100. Since claim 22 is limited to a contrast medium containing L-selectin, it would be impossible for the claimed contrast medium to detect/visualize any other ligand, such as a ligand on a leukocyte.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 4-6, 10, 14, 16-17 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Klaveness et al (WO98/18501).

Klaveness et al teach targetable gas filled microbubbles. The targeting, vector moiety of Klaveness et al corresponds to the instant receptor or L-selectin. See

teachings at page 50 of L-selectin as a vector type. The microbubbles of Klaveness et al correspond to the signal unit of instant claims 1, 10 and 22.

As to the coupling of the L-selectin vector and the microbubble, note that Kleeveness et al teach coupling through non-covalent interactions, such as avidin-biotin binding (page 30, lines 30-36; page 32, lines 28-37; and page 33, line 34.

With respect to the limitation of instant claims 1 and 22 concerning the C-terminal of the L-selectin, the examiner properly gives this no weight at all; as noted supra, in the 112, first para. enablement rejections, applicant's disclosure has not shown how to achieve coupling of avidin or biotin to only the C-terminal end of the L-selectin. The disclosure of applicant in this respect shows no more than the disclosure of Klaveness et al. The latter is as much enabled as the former and thus properly anticipates this aspect of claims 1 and 22.

Regarding the limitation of instant claim 1 concerning the N-terminal of the signal unit (reporter), the examiner likewise gives this no weight; as noted supra, in the 112, first and second paragraph rejections, the examiner is completely baffled as to how one could envision the N-terminal of a microparticle, a chelator, a dendrimer, or a gas filled microbubble. The microbubble of Klaveness et al has as much of an "N-terminal" as does any microbubble of applicant. This aspect of claim 1 is thus properly anticipated.

With respect to the "pointed away from the signal unit" limitation of instant claim 1, the examiner has noted supra (112, second) that this is confusing; to the extent that the examiner can understand what is conveyed, this aspect is also anticipated by Klaveness et al; any biotinylated microbubble, for example, would have its biotinyl

groups on the surface – i.e. "pointed away from "the microbubble. See page 47 for teaching of reagents that can be used in the "preparation of biotinylated liposmes". Klaveness et al thus teach all aspects of claim 1 with a disclosure that is enabled to the same extent as applicant's.

Regarding dependent claim 14, note teaching at page 34, lines 33-34 that "radioactive units may be readily incorporated in or attached to the reporter units". Claims 16-17 are included since the biotin would serve as a "coupling group".

Claims 1, 4-6, 10, 14, 16-17 and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Klaveness et al (WO 98/18498).

WO 98/18498 teaches essential the same as WO 98/18501 cited supra. See for example pages 20, 31, 32, 40 and 47. Claims are rejected with like rational stated supra for WO 98/18501.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness et al (WO 98/18501 or WO 98/18498) in view of Tedder et al (5,808,025).

Tedder et al teach chimeric selectins that include the carbohydrate binding receptor site of L-selectin. For example, see col.5, lines 19-20. They also teach that the taught chimeric selectins can be fused to an IgG; see col.11, lines 12-25. Since

they teach therein that an " immunoglobulin-like dimmer" is formed, it is taken that such a construct would be consistent with the limitations of both of instant claims 2-3. Tedder et al also teach that the L-selectin constructs, including those fused to a "carrier protein" (of which IgG is disclosed as an example of at col.11, lines 18-19), can be used to image sites of inflammation; see col.11 line 56-col.12, line 27.

Klaveness et al have been noted supra for teaching imaging constructs in which an L-selctin targeting moiety is coupled, via biotin – avidin binding, to a reporter that is a gas filled microbubble. These constructs have been considered as consistent with instant claims 1 and 4.

Since Tedder et al teach that their L-selectin chimeras fused to an IgG have a higher avidity (col.11, line 25) because of their dimeric structure, one would have been motivated to use such fused L-selectin proteins as the L-selectin targeting moiety in the imaging agents taught by Klaveness et al.

In an obviousness rejection that is stated on a basis separate from that pertaining to claims 2-3, the examiner also notes Tedder et al for teaching various labels for their L-selectin constructs. It has been noted supra that Klaveness et al teach provision of radioisotopes in their microbubbles. Tedder et al teach (col.12, lines 6+) that radioisotopes include 123- or 131 – Iodine. Hence the limitations of claim 13 would have been obvious.

Claims 1, 8-12 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness et al (WO 98/18501 or WO 98/18498) in view of Unger et al (6,521,211).

Klaveness et al have been noted supra for teaching targeted gas-filled microbubbles that are consistent with instant claims 1 and 10. Unger et al teach that such microbubbles may contain agents which provide contrast, besides the microbubble per se. They teach paramagnetic contrast agents at col.68, lines 31-51. These teachings are consistent with the "signal unit" of instant claims 11-12.

Regarding instant claims 7-9, note that Unger et al teach supramagnetic contrast agents, which are composed of iron oxide and which are "particulate"; see col.69, line 63-col.71, line 10. note especially col. 70, lines 36-42.

Regarding claim 14, note, col. 72 lines 43+.

Use of any of these taught additional contrast agents in the microbubble constructs of Klaveness et al would have been obvious.

Claims 1, 10 and 13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Klaveness et al (WO 98/18501 or WO 98/18498) in view of Eaton et al (4,717,657).

Klaveness et al have been noted supra for teaching targeted microbubbles consistent with instant claims 1 and 10. They teach (page 34, line 32) that such microbubbles can contain x-ray contrast media. Eaton shows that it is well known that such media contain iodine (col.1, lines 6+). Hence all limitation of instant claim 13 would have been obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Saunders, PhD whose telephone number is

571-272-0849. The examiner can normally be reached on Monday-Thursday from 8:00a.m to 5:30p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A Saunders

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March 1, 2005

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